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Delay in chemotherapy administration impacts survival in elderly patients with epithelial ovarian cancer

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HIGHLIGHTS

- In an elderly population of women with ovarian cancer, delay in chemotherapy was associated with a decreased overall survival.
- Severe anemia and neutropenia were the common reasons for dose delay.

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ABSTRACT

Objectives. The objective of this study was to characterize chemotherapy treatment patterns in elderly patients with epithelial ovarian cancer (EOC) and their impact on overall survival (OS).

Methods. We identified patients age ≥65 years with stage II–IV EOC who underwent cytoreduction from 2003 to 2011. Relevant clinical variables were extracted and correlated with OS. Statistical analyses were performed using logistic regression, Kaplan–Meier methods, and multivariable Cox proportional hazard models.

Results. One hundred and eighty-four patients were included in the analysis. The average age was 73 years with American Society of Anesthesiology Physical Status Class 2 or 3. Approximately 78% underwent primary debulking surgery (PDS). OS for the entire cohort was 3.3 years. One hundred and fifty-seven patients received adjuvant chemotherapy, of which 70% received initial platinum-based doublet therapy; 67.5% of patients were able to complete the intended six cycles of chemotherapy; of these, 34% experienced a dose reduction and 45% experienced one or more dose delays. Any dose delay was associated with a decrease in overall survival ($p = 0.02$) and remained significant even after controlling for age, stage, and residual disease and number of chemotherapy cycles received ($p = 0.029$).

Conclusions. Elderly EOC patients frequently required chemotherapy dose reductions and delays in chemotherapy administration. Multivariate analysis confirmed that dose delays are an independent factor associated with decreased OS.

1. Introduction

Elderly patients with epithelial ovarian cancer (EOC) frequently demonstrate poor outcomes when compared to their younger counterparts [1–11]. Age appears to be an independent prognostic factor associated with decreased overall survival; the mechanisms underlying this observation are not clearly defined. Plausible explanations include differences in tumor biology, inherent resistance to chemotherapy, comorbid conditions and patient choices regarding treatment and quality of life.

In addition, treatment biases in patterns of care may contribute to disparate outcomes. Patients who are perceived to be elderly or frail may receive less aggressive surgery, non-standard chemotherapy regimens, or may be provided less opportunity to participate in clinical trials [4,6,8,12]. For instance, while it is well established that platinum-based adjuvant chemotherapy improves progression-free and overall survival and is therefore standard of care for treatment of EOC [13–16], elderly EOC patients frequently do not receive standard doublet chemotherapy [8,12,15–23]. Therefore, while intrinsic patient factors contribute to decreased overall survival, there is likely an effect related to differences in patient treatment. It is unknown how differences in chemotherapy administration contribute to overall survival.

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Multiple studies have demonstrated safety and tolerability of combination platinum chemotherapy in elderly patients; however, this population is also more likely to experience delays in chemotherapy administration and reduction of delivered dose intensity (dose delay and dose reduction) [2,8,12,15,24,25]. The effect of dose delay and reductions has been difficult to interpret. Studies have demonstrated that prolonged time to adjuvant chemotherapy from surgery adversely affects survival, however there is conflicting data on the impact of delays between adjuvant chemotherapy cycles and their impact on survival [26,27]. An analysis of 157 patients with primary epithelial ovarian, fallopian tube or peritoneal carcinoma by Nagel et al. determined no significant difference in overall or progression free survival between patients who had dose delays; other authors have demonstrated that reduction to less than 70% of the total intended therapy has a deleterious impact on overall survival [28–30]. However, this has not been well studied in patients over the age of 65.

The management of ovarian cancer in the elderly patients represents an imminent health priority and challenge for gynecologic oncologists. Currently, 45% of female cancer diagnoses occur in patients greater than age 65 and this number is projected to increase [1]. Given the relative paucity of data on the impact of chemotherapy modification in elderly patients, we sought to evaluate the impact of dose delay and dose reduction on overall survival in the elderly, with a secondary intention of elucidating clinical factors useful in predicting chemotherapy tolerability.

2. Methods

Approval to conduct this study was obtained from our hospital's institutional review board. All patients with pathologically confirmed stage II to IV epithelial ovarian, fallopian tube, and primary peritoneal cancer (grouped as EOC) treated at our institution between January 2003 and December 2011 were retrospectively identified from our tumor registry. Patients were required to have undergone cytoreductive surgery performed at our institution, high grade epithelial histology, and have received first-line chemotherapy with a platinum and taxane based regimen. Patients with tumors of low malignant potential, additional synchronous primaries, non-epithelial histology or non-ovarian malignancy were excluded.

Data were abstracted from patient records. Demographic information included age at diagnosis and ethnicity. Comorbidities were captured using the American Society of Anesthesiologist Physical Status classification, which is used to assess the patient's physical state prior to surgery and is also a validated tool for use in statistical analysis and demographic data. This system stratifies patients by classes, ranging from ASA Class I (normal healthy patient without organic, physiologic or psychiatric disturbance) to Class V (moribund patients with imminent risk of death). Surgical and pathology data obtained included date of diagnosis, date of surgery, FIGO stage, tumor histology, tumor grade and residual disease (<1 cm, > or = 1 cm, and no gross residual). Chemotherapy data obtained included chemotherapy recommended, chemotherapy agents administered, recommended schedule and dosing, date of first cycle, number of cycles administered and route of administration. Chemotherapy dose delay or dose reduction was obtained and the number of cycles delayed or modified was also noted. Chemotherapy toxicity, reasons for dosage modification, need for blood transfusions and use of granulocyte colony stimulating factor were also recorded for each patient. Date of progression (as indicated by provider report, physical exam findings, doubling of CA-125 or disease progression on imaging in accordance to RECIST criteria), date of last follow-up and date of death were recorded for each patient.

Overall survival was calculated as the time from surgery until the date of death, with patients still alive censored on the date of last follow-up. Crude survival time estimates were calculated using Kaplan and Meier method. Cox proportional hazards models were used to estimate hazard ratios and to adjust for confounders. The overall adjusted effect of delays and dose modifications on OS were made through a likelihood ratio test, which compared nested models with and without treatment delay and reductions. Model assumptions, including proportional hazards and covariate functional form were reviewed for all final models.

3. Results

A total of 184 patients met the inclusion criteria. The study population age ranged from 65 to 85 years, with a median age of 72. One hundred and seventy three (94%) patients were white 90 patients (49%) were ASA Class 2 and 85 patients (47.8%) were ASA Class 3 (Table 1).

The majority of patients (92%) had advanced stage disease. Ninety eight patients, (53%) had Stage IIIC and 57 patients (31%) had Stage IV disease. The predominant tumor histology was serous (131,71%), followed by endometrioid (10, 5.4%), clear cell (6, 3.3%), mucinous (2, 1%) and mixed (35, 19%). One hundred and forty-five patients underwent primary debulking surgery (PDS). In this group, 91 patients (63%) were optimally cytoreduced to less than 1 cm of residual tumor and 24 patients (16%) to no residual disease. Thirty-nine patients underwent neoadjuvant chemotherapy/interval debulking surgery (NACT/IDS); of these 28 (72%) patients were optimally cytoreduced and 5 (13%) were cytoreduced to no residual disease (Table 1). The average time to chemotherapy following surgery was 34.4 days, with median time of 17 days (Table 2).

Chemotherapy administration, completion and dose modification data were available for 157 patients. The remaining patients either declined further chemotherapy, received chemotherapy at an outside institution or data were missing. Of 157 patients, 124 (79%) were treated with IV carboplatin/paclitaxel, 17 patients received single agent platinum therapy, and 8 patients received a platinum based doublet or triplet protocol. The regimens for these eight patients are as follows: carboplatin/paclitaxel/bevacizumab (n = 3), carboplatin/gemcitabine/

Table 1
Clinical characteristics of elderly cohort with epithelial ovarian cancer.

Variable	N = 184
Median age	72 (65–85)
Race	
White	173 (94%)
Hispanic	5 (2.7%)
Non-Hispanic black	2 (1.1%)
Asian	2 (1.1%)
ASA class	
I	3 (1.6%)
II	90 (49%)
III	88 (47.8%)
IV	3 (1.6%)
FIGO STAGE	
IIA	1 (1%)
IIB	1 (1%)
IIC	12 (6%)
IIIA	5 (3%)
IIIB	10 (5%)
IIIC	98 (53%)
IV	57 (31%)
Tumor histology	
Serous	131 (71.2%)
Endometrioid	10 (5.4%)
Clear cell	6 (3.3%)
Mucinous	2 (1.1%)
Mixed/other	35 (19%)
Primary cytoreduction	*N = 145*
> or = 1 cm	30 (21%)
<1 cm	91 (63%)
No gross residual	24 (16%)
Interval cytoreduction	*N = 39*
> or = 1 cm	6 (15%)
<1 cm	28 (72%)
No gross residual	5 (13%)